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Letters to the Editor

Dear Editor

Quality of life in a cross-over design

As a parameter, quality of life (QOL) has become more common in clinical trials. The focus has been on the reliability and validity of the chosen tests, their ability to discriminate between different groups of respondents, and administrative simplicity. Less attention has been paid to the design and methodology of the study.

Impaired QOL should be a part of the inclusion criteria. The randomized groups should be comparable. The duration of treatment should be long enough to make sure that an effect is possible. In a cross-over study, the washout period should be long enough to remove any carry-over effect. The required washout period can be difficult to predict, and may differ for various parameters of QOL. This is one of our conclusions from a clinical trial (1).

In this cross-over trial, salmeterol was compared with salbutamol controlled release (salb. CR) in 59 asthmatic patients. Carry-over effect was found for QOL, but not for peak expiratory flow rate, symptom score or additional use of salbutamol. Analyses were carried out on three scores derived from the 'Living With Asthma Questionnaire' (LWAQ): (1) the overall score (OS); (2) the problem subscale score (PSS); and (3) the evaluation subscale score (ESS) (2).

When results were analysed without reference to the order of treatment, we found that, for OS and PSS, there was a significant difference between run-in and salmeterol and between run-in and salb. CR, but there was no difference between salmeterol and salb. CR. However, there was also a significant difference between run-in and washout, suggesting either a trial effect or some carry-over effect from the active treatment. In the case of ESS, the only significant difference was between run-in and salmeterol.

When the order of treatment was taken into account, we found a significant effect of treatment order for the ESS. This was not the case for OS and PSS. The results show that patients treated initially with salmeterol showed an improvement on the ESS, but those treated initially with salb. CR did not show an improvement, in fact there was a non-significant deterioration. The reason for this finding is not clear but one possibility could be that the initial treatment with salb. CR, in spite of the washout period, prevented the positive effect of salmeterol. This possibility should be treated with caution and, at this stage, should only be considered as an area for further investigation.

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Dear Editor

Pulmonary alveolar proteinosis and disseminated *Mycobacterium avium* infection

Pulmonary alveolar protelnosis (PAP) is a rare disorder characterized by accumulation of phospholipidic material in the alveolar space (1), which can be 'idiopathic' or secondary to various conditions, such as malignant haematologic disorders (2). Recently, isolation of *Mycobacterium avium intra cellulare* (MAI) has been reported in patients with PAP, suggesting that defective alveolar macrophage function linked to PAP contributed to the higher frequency of pulmonary MAI infection (3). As a further contribution, we report a woman with PAP and a MAI bone-marrow and lymph-node infection but without MAI pulmonary involvement.

We have previously reported the case of a 32-year-old female (4) who developed fever, weight loss, cervical lymph nodes and pancytopenia (white blood cells count: $1{\cdot}8 \times 10^9\,l^{-1}$ with 63% neutrophils, 25% lymphocytes, 5% monocytes, 5% eosinophils; haemoglobin $7{\cdot}8$ g dl^{-1}; platelets $135 \times 10^{12}\,l^{-1}$). Numerous caseous necrotic granuloma were seen in the lymph nodes and bone marrow with Ziehl-Nielsen positive bacilli. Culture of bone marrow was positive for MAI. Chest X-ray studies showed a miliary pattern. Bronchoalveolar lavage and sputum culture were negative for mycobacteria as well as for other pathogens. No acquired illness or primary immunodeficiency was found that could explain this

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